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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/083,336	02/27/2002	Mark A. Olson	P67452US0 (RIID 01-58)	8239

7590

09/24/2003

ATTN: MCMR-JA (Ms. Elizabeth Arwine)
Office of the Staff Judge Advocate
U.S. Army Medical Research and Materiel Command
504 Scott Street
Fort Detrick, MD 21702-5012

EXAMINER

RAO, MANJUNATH N

ART UNIT PAPER NUMBER

1652

DATE MAILED: 09/24/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No. 10/083,336	Applicant(s) OLSON ET AL.	
	Examiner Manjunath N. Rao, Ph.D.	Art Unit 1652	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 23 June 2003.
- 2a) ☐ This action is **FINAL**. 2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 1-10, 14-18 and 24 is/are pending in the application.
- 4a) Of the above claim(s) 18 is/are withdrawn from consideration.
- 5) ☐ Claim(s) _____ is/are allowed.
- 6) ☒ Claim(s) 1-10, 14-17 and 24 is/are rejected.
- 7) ☐ Claim(s) _____ is/are objected to.
- 8) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☒ The drawing(s) filed on 27 February 2002 is/are: a) ☒ accepted or b) ☐ objected to by the Examiner.
- Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
- 11) ☐ The proposed drawing correction filed on _____ is: a) ☐ approved b) ☐ disapproved by the Examiner.
- If approved, corrected drawings are required in reply to this Office action.
- 12) ☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

- 13) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some * c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. _____.
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).
- * See the attached detailed Office action for a list of the certified copies not received.
- 14) ☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).
- a) ☐ The translation of the foreign language provisional application has been received.
- 15) ☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

- | | |
|---|---|
| 1) <input checked="" type="checkbox"/> Notice of References Cited (PTO-892) | 4) <input type="checkbox"/> Interview Summary (PTO-413) Paper No(s). _____ |
| 2) <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948) | 5) <input type="checkbox"/> Notice of Informal Patent Application (PTO-152) |
| 3) <input checked="" type="checkbox"/> Information Disclosure Statement(s) (PTO-1449) Paper No(s) <u>6, 8, 10</u> | 6) <input type="checkbox"/> Other: _____ |

DETAILED ACTION

Claims 1-10, 14-18, 24 are currently pending in this application. Claims 1-10, 14-17, and 24 are now under consideration. Claim 18 remains withdrawn from consideration as being drawn to non-elected invention. Examiner regrets the inadvertent inclusion of claim 18 in group I in the previous Office action. This claim drawn to an antibody should have been included in group III drawn to antibody. As for claim 24 only part (a) and (c) drawn to a kit comprising the polypeptide portion has only been examined.

Election/Restrictions

Applicant's election without traverse of Group I in Paper No. 9 is acknowledged.

Drawings

Drawings submitted in this application are accepted by the Examiner for examination purposes only.

Claim Objections

Claim 24 is objected to because of the following informalities: Claim 24 continues to be directed to non-elected subject matter (i.e., antibody or vaccine). Appropriate correction is required.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

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The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claim 1, 24 and claims 2-10, 14-17 which depend from claim 1 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Claim 1 recites the phrase "having substantial identity to". The metes and bounds of this phrase are not clear to the Examiner. A perusal of the specification did not provide a definition for the above phrase. It is not clear to the Examiner as to how much identity to the wild type is considered by the applicant as "substantial identity". Without a definitive numerical value associated with it, the above phrase renders the claim indefinite. Correction is required.

Claim 1, 24 and claims 2-10, 14-17 which depend from claim 1 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Claim 1 recites the phrase "reduced N-glycosidase-rRNA activity as compared to a control". Here again the metes and bounds of the above phrase are not clear to the Examiner. Specifically, it is not clear to the Examiner as to which polypeptide is considered as "a control". If applicants are comparing the variant to a wild type (as a control), they must recite it in the claim. Without such definitive recitation, the above claim remains unclear to the Examiner.

Claim 2 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Claim 2 recites the phrase "functional integrity". The meaning of the above phrase

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in the context of the above claim is not clear to the Examiner. Examiner suggests deletion of the above phrase.

Claims 4-5 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Claims 4 and 5 recite the phrase "or a variant thereof". This phrase appears to be redundant and does not in a way limit claim 1 any further. This is because claim 1 is already drawn to a "variant". It appears that applicants are claiming a variant of a variant which does not actually make it very clear as to what exactly they are intending to claim. Correction is required.

Claim 6 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Claim 6 recites the phrase "substantially identical". The metes and bounds of the above phrase are not clear to the Examiner. A perusal of the specification does not provide a specific definition for the above phrase. Without a numerical value associated with the above phrase, the claim is rendered indefinite. Correction is required.

Claim 7 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Claim 7 recites the phrase "that corresponds to the hydrophobic loop". The meaning of the above phrase in the context of the above claim is not clear to the Examiner, specifically

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the terms "corresponds to" rendering the claim unclear. Examiner suggests deletion of the entire phrase. Correction is required.

The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-10, 14-17 and 24(a), (c) are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a ricin polypeptide with SEQ ID NO:1 through 4 having some properties of wild type ricin A, does not reasonably provide enablement for any variant lacking N-glycosidase-rRNA activity or having reduced activity and higher solubility than wild type ricin A chain or lacking the hydrophobic loop of wild type ricin or any polypeptide that is substantially identical to SEQ ID NO:1-4. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make the invention commensurate in scope with these claims.

Factors to be considered in determining whether undue experimentation is required, are summarized in *In re Wands* (858 F.2d 731, 8 USPQ 2d 1400 (Fed. Cir. 1988)) as follows: (1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claim(s).

Claims 1-10, 14-17 and 24(a), (c) are so broad as to encompass any ricin polypeptide variant having no activity or reduced N-glycosidase activity. The scope of the claims is not

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commensurate with the enablement provided by the disclosure with regard to the extremely large number of variants broadly encompassed by the claims. Since the amino acid sequence of a protein determines its structural and functional properties, predictability of which changes can be tolerated in a protein's amino acid sequence and obtain the desired activity requires a knowledge of and guidance with regard to which amino acids in the protein's sequence, if any, are tolerant of modification and which are conserved (i.e. expectedly intolerant to modification), and detailed knowledge of the ways in which the proteins' structure relates to its function. However, in this case the disclosure is limited to the encoded amino acid sequence of only four variants. It would require undue experimentation of the skilled artisan to make and use the claimed polypeptides with an undefined function/activity. The specification is limited to teaching the use of SEQ ID NO: 1-4 as ricin variants having reduced or absent N-glycosidase activity (but probably having other properties such as internalization) but provides no guidance with regard to the making of variants and mutants or with regard to other uses. In view of the great breadth of the claim, amount of experimentation required to make the claimed polypeptides, the lack of guidance, working examples, and unpredictability of the art in predicting function from a polypeptide primary structure (e.g., see Ngo et al. in *The Protein Folding Problem and Tertiary Structure Prediction*, 1994, Merz et al. (ed.), Birkhauser, Boston, MA, pp. 433 and 492-495, Ref: U, Form-892), the claimed invention would require undue experimentation. As such, the specification fails to teach one of ordinary skill how to use the full scope of the polypeptides encompassed by this claim.

While recombinant and mutagenesis techniques are known, it is not routine in the art to screen for multiple substitutions or multiple modifications, as encompassed by the instant claims,

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and the positions within a protein's sequence where amino acid modifications can be made with a reasonable expectation of success in obtaining the desired activity/utility are limited in any protein and the result of such modifications is unpredictable. In addition, one skilled in the art would expect any tolerance to modification for a given protein to diminish with each further and additional modification, e.g. multiple substitutions.

The specification does not support the broad scope of the claims which encompass all modifications and fragments of wild type ricin and that of SEQ ID NOS:1-4 because the specification does not establish: (A) regions of the protein structure which may be modified such that it affects activity; (B) the general tolerance of ricin polypeptides to modification and extent of such tolerance; (C) a rational and predictable scheme for modifying any amino acid residue with an expectation of obtaining the desired biological function; and (D) the specification provides insufficient guidance as to which of the essentially infinite possible choices is likely to be successful.

Thus, applicants have not provided sufficient guidance to enable one of ordinary skill in the art to make and use the claimed invention in a manner reasonably correlated with the scope of the claims broadly including variants with an enormous number of amino acid modifications of the ricin and of SEQ ID NOS:1-4. The scope of the claims must bear a reasonable correlation with the scope of enablement (*In re Fisher*, 166 USPQ 19 24 (CCPA 1970)). Without sufficient guidance, determination of polypeptides having the desired biological characteristics is unpredictable and the experimentation left to those skilled in the art is unnecessarily, and improperly, extensive and undue. See *In re Wands* 858 F.2d 731, 8 USPQ2d 1400 (Fed. Cir, 1988).

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Claims 1-3, 8-10, 14-17, 24 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Claims 1-3, 8-10, 14-17, 24 are directed to ricin polypeptide variants having reduced N-glycosidase activity or no N-glycosidase activity with neutralizing epitope and greater solubility compared to wild type ricin. Claims 1-3, 8-10, 14-17, 24 are rejected under this section of 35 USC 112 because the claims are directed to a genus of polypeptides including modified polypeptide sequences, modified by at least one of deletion, addition, insertion and substitution that have not been disclosed in the specification. No description has been provided of the modified polypeptide sequences encompassed by the claim. No information, beyond the characterization of SEQ ID NO:1-4 has been provided by applicants which would indicate that they had possession of the claimed genus of modified polypeptides. The specification does not contain any disclosure of the structure of all the polypeptide sequences including fragments and variants within the scope of the claimed genus. The genus of polypeptides claimed is a large variable genus including peptides which can have a wide variety of structures. Therefore many structurally unrelated polypeptides are encompassed within the scope of these claims. The specification discloses only 4 species of the claimed genus which is insufficient to put one of skill in the art in possession of the attributes and features of all species within the claimed genus. Therefore, one skilled in the art cannot reasonably conclude that applicant had possession of the claimed invention at the time the instant application was filed.

Applicant is referred to the revised guidelines concerning compliance with the written description requirement of U.S.C. 112, first paragraph, published in the Official Gazette and also available at www.uspto.gov.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless –

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 1-10 are rejected under 35 U.S.C. 102(b) as being anticipated by Gould et al. (Mol. Genet, 1991, Vol. 230:81-90) or Bradley et al. (Int. J. Peptide Protein Res., 1989, Vol. 34 :2-5) or Frankel et al. (Mol. Cell. Biol., 1989, Vol. 9(2):415-420) or Kim et al. (Protein Engg., 1992, Vol. 5(8) :775-779) (all refs in IDS) or Walsh et al. (US 5,635,384, 6-3-1997). This rejection is based upon the public availability of a printed publication more than one year before the date of the filing of the instant application. Claims 1-10 of the instant application are drawn to variant ricin polypeptide having no N-glycosidase or reduced N-glycosidase activity, having neutralizing immunological epitope and a solubility greater than solubility of wild type ricin, substantial identity with SEQ ID NO:2-4 or variants thereof lacking hydrophobic loop made by cleaving the globular domain or, made by recombinant methods. Gould et al., Bradley et al., Frankel et al., Walsh et al. and Kim et al. independently disclose a ricin variants with reduced or absent N-glycosidase activity. All the above references may not explicitly disclose the polypeptides as having neutralizing immunological epitope and a solubility greater than

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solubility of wild type ricin or substantial identity with SEQ ID NO:2-4 or that as lacking hydrophobic loop. However, as applicants are claiming variants with no limitation placed on the number of changes that can be present in the polypeptide sequence, claims 1-10 read on the polypeptide sequences disclosed by Gould et al., Bradley et al., Frankel et al., Walsh et al. and Kim et al.. Thus Gould et al., Bradley et al., Frankel et al., Walsh et al. and Kim et al. anticipate claims 1-10 of this application as written.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

Claims 14-17 and 24 are rejected under 35 U.S.C. 103(a) as being unpatentable over Gould et al., Bradley et al., Frankel et al., Walsh et al. and Kim et al. as applied to claims 1-10 above, and further in view of the common knowledge in the art. Claims 14-17 and 24 are drawn to pharmaceutical compositions comprising the above polypeptide variants and a kit comprising the variant polypeptide.

The references of Gould et al., Bradley et al., Frankel et al. and Kim et al. as it applies to variant ricin has been discussed above. While the above references do not teach the making of a pharmaceutical compositions or a kit comprising the variant polypeptides, combining the above teachings of the above references and the common knowledge in the art that ricin polypeptide is a highly toxic compound which has military applications, it would have been

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obvious to those skilled in the art to use the variants with reduced or absent N-glycosidase activity and retained neutralizing immunological epitope to develop vaccine compositions. Those skilled in the art would have been motivated to do so due to commercial value of the products (vaccines and Kits comprising the antigen or variant polypeptides) developed using the variant polypeptides. Those skilled in the art would have a reasonable expectation of success because the above references provide ricin polypeptides with up to 1000 fold reduced activity.

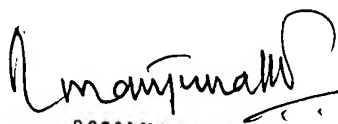
Therefore the above invention would have been *prima facie* obvious to those skilled in the art.

Conclusion

None of the claims are allowable.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Manjunath N. Rao, Ph.D. whose telephone number is 703-306-5681. The examiner can normally be reached on 7.30 a.m. to 4.00 p.m. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ponnathapura Achutamurthy can be reached on 703-308-3804. The fax phone numbers for the organization where this application or proceeding is assigned are 703-308-4242 for regular communications and 703-308-4242 for After Final communications. Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 703-306-0196.

Manjunath N. Rao
September 17, 2003


MANJUNATH RAO
PATENT EXAMINER